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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/784,911	HARRISON ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the "Amendment under 37 C.F.R. §1.116" of 17 February 2004 filed in response to the Final Office Action mailed 12 August 2003. Claims 1-5, 8-15 and 30-32 were considered in the 12 August Office Action. Claims 23-32 were canceled and claims 1, 4, 5, 12 and 15 were amended. Claims 1-5 and 8-15 are pending and under consideration. Finality of the previous Office Action is hereby withdrawn in view of the new grounds for rejection set forth herein below.

Response to Amendment

Objections and rejections set forth against claims 30-32 are rendered moot in view of cancellation thereof.

Claim Rejections - 35 USC § 112

Rejection of claims 1-3, 5, 8, 9 and 11-14 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter is withdrawn in view of the amendments to the claims.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 8-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating growth and differentiation of mammalian pancreatic cells into three-dimensional cystic-ductular structures containing insulin-secreting cells wherein said mammalian pancreatic cells are isolated from fetal pancreata as set forth in Example 4, does not reasonably provide enablement for the method wherein the pancreatic cell is any precursor cell which is acted upon by a BMP as defined in the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a method of differentiating cells into structures resembling pancreatic ducts and capable of secreting insulin. Although the claims recite that the starting material is "pancreatic epithelial cells" or "pancreatic cells", the specification provides a broad definition of "pancreatic cell", which encompasses any

precursor cell. The definition of pancreatic cells is set forth in the fourth paragraph on page 12 of the specification and reads as follows (emphasis added):

> The term "pancreatic cells" is used herein in its broadest context to include any pancreatic or precursor cell which is acted upon by a BMP... Examples of such cells include progenitor cells, stem cells, duct cells or any other cell precursor. Reference to "progenitor cells" and "stem cells" includes any embryonic stem (ES) cell committed to a pancreatic cell lineage. All such cell types are encompassed by the term "pancreatic cells" or "pancreatic cell".

Thus, the specification defines "pancreatic cells" as including any precursor cell, which can be a precursor of any cell type.

State of the prior art and level of predictability in the art: With regard to precursor cells other than those found within the pancreas, the art teaches that, at the time of filing, practicing the claimed method using precursor cells other than those residing in the pancreas was highly unpredictable. *Stem Cells: Scientific Progress and Future Research Directions*. Department of Health and Human Services. June 2001. http://www.nih.gov/news/stemcell/scireport.htm (hereinafter, *Stem Cells*) teaches, "[a]n adult stem cell is an undifferentiated (unspecialized) cell that occurs in a differentiated (specialized) tissue, renews itself, and becomes specialized to yield all of the specialized cell types of the tissue from which it originated" (paragraph bridging pages ES-2 to ES-3). *Stem Cells* further teaches that adult stem cells have been derived from brain, bone marrow, peripheral blood, dental pulp, spinal cord, blood vessels, skeletal muscle, epithelia of the skin and digestive system, cornea, retina, liver and pancreas (fourth full paragraph in the right column on page 37). With regard to plasticity of adult stem cells, *Stem Cells* teaches, "[t]he concept of adult stem cell plasticity is new, and the phenomenon is not thoroughly understood" (first full paragraph on page ES-3). Although there is some evidence that some adult stem cells

are capable of being genetically reprogrammed to generate specialized cells, *Stem Cells* teaches, "[c]urrent evidence indicates that the capability of adult stem cells to give rise to many different specialized cell types is more limited than that of embryonic stem cells" (paragraph bridging pages ES-9 to ES-10). *Stem Cells* teaches, "[c]ollectively, studies on plasticity suggest that stem cell populations in adult mammals are not fixed entities, and that after exposure to a new environment, they may be able to repopulate other tissues and possibly differentiate into other cell types" (first full paragraph on page 28) however, "it is not yet clear to what extent plasticity can occur in experimental settings" (paragraph bridging the left and right columns on page 28).

Given the teachings of *Stem Cells*, the skilled artisan would not expect that the claimed method could be readily practiced using stem cells obtained from brain, bone marrow, peripheral blood, dental pulp, spinal cord, blood vessels, skeletal muscle, epithelia of the skin and digestive system, cornea, retina and liver. Thus, the skilled artisan must rely on the teachings of the instant specification to describe the process of practicing the claimed method using the broad scope of any progenitor cell in full, clear, concise, and exact terms such that the skilled artisan could practice the full scope of the claimed invention without undue experimentation.

With regard to embryonic stem cells, which are also reasonably encompassed by the "pancreatic cells" of the claims in view of the definition set forth in the specification, the art provides no guidance as to how one might establish three-dimensional cystic-ductular structures containing insulin-secreting cells from ES cells. The art recognizes that, although cells having phenotypic characteristics of a variety of cell types have been produced from ES cells *in vitro* (see *Stem Cells*, page 8, Table 2.1), *Stem Cells* teaches, "[i]t is not possible to explain *how* the directed differentiation occurs...No one knows how or when gene expression is changed, what

signal-transduction systems are triggered, or what cell-cell interactions must occur to convert undifferentiated ES cells into precursor cells and, finally, into differentiated cells that look and function like their *in vivo* counterparts" (bridging pages 7-8). Thus, the art teaches that although ES cells are pluripotent, the *in vitro* production of any given cell type from an ES cell requires proper manipulation of culture conditions. Furthermore, the art teaches that, at the time of filing, it was not possible to predict what manipulations would be required to produce any given cell type based on experience obtained producing other cell types from ES cells.

Amount of direction provided by the inventor and existence of working examples: The specification provides a single example of cells capable of forming three-dimensional cystic-ductular structures containing insulin-secreting cells when cultured in the presence of bone morphogenetic protein and laminin-1 (*i.e.,* the dissociated fetal pancreas cells produced in Example 4; see also Example 24). The specification is silent with regard to establishing three-dimensional cystic-ductular structures containing insulin-secreting cells from cells obtained from any organ other than pancreas, including embryonic stem cells.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to practice the full scope of the instant claims without engaging in undue experimentation. The art recognizes that precursor cells found in various organs are not equivalent in their potential to form structures that are characteristic of any given organ or tissue. That is, the art does not recognize that all progenitor cells are pluripotent as the term is defined in the first paragraph in the right column on page 1 of *Stem Cells*, and the skilled artisan would not expect that the method steps set forth in the claims would produce three-dimensional cystic-

ductular structures containing insulin-secreting cells regardless of the progenitor cell used. Likewise, the skilled artisan would not expect that simply culturing ES cells in the presence of a bone morphogenetic protein and at least one of laminin-1 or lamin-1-containing extracellular matrix would produce three-dimensional cystic-ductular structures containing insulin-secreting cells. Therefore, in order to practice the full scope of the claimed invention, the skilled artisan would have to resort to empirical experimentation to devise culture conditions which, in addition to culturing in the presence of a bone morphogenetic protein and at least one of laminin-1 or lamin-1-containing extracellular matrix, would produce three-dimensional cystic-ductular structures containing insulin-secreting cells from each of the cell types encompassed by the "pancreatic cells" of the claims. Thus, practicing the method according to the full scope of the claims would clearly require undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in the recitation of "pancreatic lineage embryonic stem cells". *Stem Cells* states, "[p]luripotency—that is the ability to give rise to differentiated cell types that are derived from all three primary germ layers of the embryo, endoderm, mesoderm and ectoderm—is what makes ES cells unique" (page 6, left column, first full paragraph). Thus, an embryonic stem cell, by definition, cannot be committed to a particular lineage because an ES

cell is pluripotent. It would seem that Applicant intends that the cell referred to is a pancreatic progenitor cell, which is recognized in the art to arise from embryonic stem cells. However, progenitor cell in the specification is also defined as an ES cell committed to a pancreatic cell lineage and simply reciting "progenitor cell" would also be indefinite in view of the definition provided in the specification.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

Anne-marie Falk

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